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LITERATURE REVIEW

The involvement of *anginosus* group streptococci in rhinosinusitis and their complications

Gabriela Bancescu[1], Manuela Radu-Popescu[2], Adrian Bancescu[3]

[1]University of Medicine and Pharmacy "Carol Davila", Bucharest, Chair MD7, Microbiology Department;

[2]University of Medicine and Pharmacy "Carol Davila", Bucharest, Chair F5, General and Pharmaceutical Microbiology Department;

[3]University of Medicine and Pharmacy "Carol Davila", Bucharest, Chair M32, Epidemiology Department

The streptococci of anginosus group belong to oral streptococci and have been known over time under different names, such as: Streptococcus milleri group, streptococci milleri, the groups F and G minute colony-forming streptococci, Streptococcus MG or group F hemolytic and non-hemolytic streptococci.

At present, the recognized name is *Streptococcus anginosus* group, and the DNA-DNA hybridization confirmed that this group comprises three distinct species: *S. anginosus*, *S. constellatus* and *S. intermedius*[1]. However, the lack of a single accepted nomenclature for these streptococci generated over time a lot of difficulties in species differentiation.

The strains of *anginosus* group streptococci are phenotypically diverse, even within the same species, but they share several characteristics: they develop small colonies with specific caramel smell, produce acetoine from glucose (positive Voges-Proskauer test) and hydrolyze arginine. The isolates are either non-hemolytic or α-hemolytic, and occasionally β-hemolytic, and are mostly non-groupable or may belong to group Lancefield: C, F, G or A[1,2].

The identification at species level, in the case of oral streptococci, by conventional diagnostic methods, is mainly based on biochemical tests and it is difficult and time-consuming. Variable results in species identification are also obtained when using different commercially available systems.

While speciation of oral streptococci by conventional biochemical tests is rather difficult, the molecular methods offer a more accurate identification at species level also within the *anginosus* group, and could reveal important characteristics of these microorganisms, contributing to a better understanding of their role in human pathology[1,3,4,5,6,7]. Several molecular techniques have been applied for species identification within the *anginosus* group, based on 16S rRNA genes, 16S-to-23S rRNA gene intergenic spacer region and the penicillin-binding protein etc. In 2010, Olsen and colab. developed some real-time PCR assays based on sequence analysis of 16S rRNA and *cpn60* gene with rapid and accurate detection of the three *anginosus* group species, either in pure cultures or in clinical samples[8]. However, accurate species identification is required to determine the real prevalence and clinical aspects of the infections produced by these bacteria.

Rapid identification at species level within the *anginosus* group relies also on detection by PCR of marker genes, like *ily* gene which is specific to *S. intermedius*. This gene encodes a human specific cytoxin that lyses human cells, named intermedilysin, which seems to be highly involved in deep-seated abscesses producing[9,10].

The streptococci of *anginosus* group are considered commensal microorganisms belonging to the oropharyngeal, gastrointestinal and urogenital flora, but may

Corresponding author: Gabriela Bancescu, Bucharest, Romania, 19-21 D. Gerota Str., District 2
email: adrianbancescu@yahoo.com

be involved in different types of oral and nonoral infections, mostly in immunocompromised patients. Although their mechanisms of pathogenicity is not very well established, it is known that some strains may possess virulence factors like: polysaccharide capsule, adherence factors, surface-protein structures with same role in virulence as M protein in S. pyogenes, hemolysins and other host tissue degradative enzymes, such as: ribonuclease, deoxyribonuclease, chondroitin sulfatase, hyaluronidase, sialidase etc. The activity of the last two enzymes was detected in strains of *S. intermedius* and sometimes in strains of *S. constellatus*, while sialidase (neuraminidase) activity was found only in *S. intermedius* strains[1].

The *anginosus* group streptococci have been frequently isolated from various oral and maxillofacial infections (e.g. abscesses developed at different oral sites, odontogenic sinusitis, sialadenitis, maxillary osteomyelitis etc.) and extra-oral diseases, such as: deep-seated abscesses, central nervous system and ophthalmic infections, ear - nose - throat infections, sepsis and cardiovascular infections, pleuropulmonary infections, abdominal infections, urogenital infections, skin and soft tissue infections and musculoskeletal infections[2,11]. The results of a Canadian study showed that this bacterial group is responsible for about 50% of all invasive pyogenic infections produced by streptococci in a large health region[12], and the findings of another recent research work indicated these bacteria as the second etiological agent of skin and soft tissue infections, just after *Staphylococcus aureus*[13].

The species belonging to the *anginosus* group are seldom isolated from infective endocarditis cases, compared to other oral streptococci[2]. Nevertheless, the bacteremia with *anginosus* streptococci is almost clinically significant and is usually suggestive for a focus of a suppurative infection, especially when persisting under proper antibiotic administration. In contrast to other viridans streptococci, this group presents a special propensity to form metastatic abscesses at many sites of the body, especially in the liver and brain. *S. constellatus* and *S. intermedius* are associated with a higher frequency than *S. anginosus* with the abscesses, and *S. intermedius* especially with the deep-seated abscesses[14].

The odontogenic or rhinogenic sinusitis should also be mentioned among the pyogenic infections caused by the *anginosus* group streptococci. Rhinosinusitis refers to infection of one or more of the paranasal sinuses (maxillary, ethmoid, frontal and sphenoid sinus) and is generally produced by microorganisms from the upper respiratory tract. The acute rhinosinusitis may be of bacterial, viral or fungal etiology, and is either community or nosocomially acquired. The nosocomial rhinosinusitis is usually a mixed infection produced mainly by: *S. aureus*, *Pseudomonas aeruginosa* and members of *Enterobacteriaceae* family, while the most common bacteria involved in the acute community acquired rhinosinusitis are *Streptococcus pneumoniae* and *Haemophilus influenzae*, accounting for half of all cases, in both children and adults, followed by *Moraxella catarrhalis*, which is more frequent in children[15,16]. The *anginosus* group streptococci were also reported among other bacterial agents isolated from rhinosinusitis, in addition to other α-haemolytic and group A streptococci, *S. aureus* and the strictly anaerobic bacteria[16].

The chronic sinusitis is caused mainly by *S. pneumoniae* and *H. influenzae*, and in a lower proportion by other microorganisms, such as: *M. catarrhalis, S. aureus, Pseudomonas* spp., strictly anaerobic bacteria and streptococci of *anginosus* group[16]. The *anginosus* group streptococci were isolated from sinus inflammatory exudates, almost in association with other bacteria, but sometimes, in pure culture too. Thus, Tran and colab. have reported invasive infections produced by *S. intermedius*, including a frontal abscess case, secondary to a chronic pansinusitis in a 16 year-old girl, and this bacteria was recognized as the only etiological agent isolated from the surgical drainage pus[17].

Of all paranasal sinuses, the maxillary sinus is the most commonly affected and about 10% of the cases are of odontogenic origin, which differ from the rhinogenic sinusitis by microbiology and physiopathology aspects[18]. The odontogenic rhinosinusitis is produced when the Schneidarian membrane is damaged and usually develops dental infections or dental and maxillary bone trauma, being frequently iatrogenic infections, post dental or surgery procedures (e.g. tooth extraction, dental implantation etc.)[19]. A five-year period Romanian statistical study on inflammatory affections of the maxillary sinus in Romanian patients revealed that the odontogenic maxillary sinusitis appeared mostly due to a periapical septic process, or in a lower proportion, to the presence of an oroantral fistula[20].

The odontogenic rhinosinusitis is often a mixed infection, involving both aerobic and anaerobic bacteria, with anaerobic streptococci and gram-negative bacilli predominating[18]. Nevertheless, Brook and colab., investigating the bacteria involved in periapi-

cal abscesses and the corresponding infected maxillary sinus, noticed that *S. milleri* was isolated only from pus aspirates from periapical abscesses and failed to be recovered from maxillary sinusitis in same patients, concluding that these streptococci might not thrive well at this anatomical site[21]. However, several other recent studies reported the role played by *S. anginosus* group in rhinosinusitis, especially in some serious complications of odontogenic rhinosinusitis, like brain abscesses[22].

The bone which harbors the paranasal sinuses represents a barrier against the microbial spreading. Despite this, the infection of paranasal sinuses may extend to the orbit and intracranial cavity, either directly or through bacteremia. The statistical data have indicated that these complications appear especially in young male adults and children. The orbital cellulitis represents about 80% of these cases, with bacteria disseminating mainly from ethmoid sinus, through lamina papyracea defects or ophthalmologic venous system. In contrast, the intracranial complications were encountered in only 13% of the cases and are mainly secondary to frontal sinusitis, while the temporal lobes and sella turcica are usually affected in the setting of sphenoid sinusitis[23]. The intracranial complications due to the paranasal sinusitis are the following, mentioned in crescent order of frequency: epidural abscess, subdural empyema, meningitis, encephalitis, brain abscess and thrombosis of the cavernous sinus[24].

Rhinosinusitis can lead to brain abscess through direct extension or hematogenous spreading via thrombophlebitis of the valveless diploic veins[25]. The subdural and extradural empyemas are mostly sinogenic complications and are often associated with *S. anginosus* positive sinus cultures[26]. However, the findings of many studies, focused on clinical-microbiological investigation in acute and chronic rhinosinusitis complications, suggest that *anginosus* group streptococci are the etiological agents most frequently involved in these infections in both children and adults, either immunodeficient or immunocompetent subjects[27,28]. Several studies reported positive cultures for *S. milleri* group streptococci in more than 30% of patients with orbital and intracranial complications. In addition, the authors of a retrospective study reviewing the acute sinusitis complications treated in a tertiary care children's hospital during a 7½-year period concluded that *S. milleri* should be considered among the common pathogens of the complications of rhinosinusitis[23].

The bacteremia with streptococci belonging to the *anginosus* group due to rhinogenic sinusitis may lead to unique or multiple brain abscesses[22], and *S. intermedius* is recognized as the principal pathogen able to produce brain abscesses, either as single etiological agent or in association with other microorganisms, especially with the strictly anaerobic bacteria[11,14,29,30,31]. However, many previous studies dealing with microbiology of brain abscesses reported the oral streptococcal isolates only as viridans streptococci, without performing species identification[32,33].

The conclusion of several studies was that oral streptococci are the most commonly bacteria isolated from brain abscesses (70% of cases), which are in 30-60% of cases mixed infections. In a retrospective case series, Bair-Merritt and colab. found a high prevalence of the *milleri* group streptococci, of approximately one third of the investigated cases of suppurative intracranial complications of rhinosinusitis in previously healthy children[34]. The results of many research works indicated that brain abscesses related to rhinosinusitis developed particularly in males between 10 and 30 years of age. Unfortunately, in about 24-40% of the intracerebral abscesses, the bacterial cultures give negative results, mostly because of antimicrobial therapy. In such cases, it is recommended to apply directly in patient samples the 16S ribosomal RNA gene amplification and sequencing, in order to reveal the etiological agent. In this way, Petti and colab. could detect streptococci of *anginosus* group in three cases of brain abscesses without positive culture results[35].

As acute rhinosinusitis is one of the most common infectious diseases, especially in children[24], and represents more than 20% of all antibiotic prescriptions in paediatric patients, the diagnosis and appropriate treatment must be performed in real time to avoid life-threatening infectious complications sometimes[23]. In intracranial complications associated to rhinosinusitis, the surgical drainage of pus is mandatory and combined with antimicrobial therapy[24].

Previously, all oral streptococci were uniformely susceptible to penicillin. At present, resistance to betalactam and other commonly used antibiotics has benn detected among the isolates of *anginosus* streptococci, too. Since these streptococci might be involved, alone or in association with other bacteria, in serious infections which need antimicrobial treatment, it is necessary to investigate their susceptibility to antibiotics.

The streptococci of *anginosus* group seem to be more involved in human pathology than they were previously appreciated and their undoubted association with rhinosinusitis and related intracranial complications should be recognized by all oto-rhino-laryngologists[26].

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